(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) **EP 2 620 171 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
06.05.2020 Bulletin 2020/19

(21) Application number: **13152312.8**

(22) Date of filing: **23.01.2013**

(51) Int Cl.:
A61M 1/34 *(2006.01)* ***A61M 1/36*** *(2006.01)*

(54) **Systems and methods for performing online extracorporeal photopheresis**

Systeme und Verfahren zur Durchführung einer gekoppelten extrakorporalen Photopherese

Systèmes et procédés permettant d'effectuer une photophérèse extracorporelle en ligne

(84) Designated Contracting States:
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR

(30) Priority: **27.01.2012 US 201261591596 P**
21.05.2012 US 201261649438 P
03.01.2013 US 201313733607

(43) Date of publication of application:
31.07.2013 Bulletin 2013/31

(60) Divisional application:
20156004.2

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Description

Field of the Disclosure

[0001] The present disclosure relates to systems and methods for performing online extracorporeal photopheresis ("ECP"). More particularly, the present disclosure is directed to systems and methods for removing mononuclear cells from a patient, treating the removed cells and returning treated cells to the patient in a single "on-line" procedure utilizing a multifunctional apheresis device, an independent and separately housed device for irradiating cells with light and a disposable processing set that provides a sterile closed pathway between the apheresis device and the irradiation device.

Background

[0002] Whole blood is made up of various cellular and non-cellular components such as red cells, white cells and platelets suspended in its liquid component, plasma. Whole blood can be separated into its constituent components (cellular, liquid or other), and the separated component can be administered to a patient in need of that particular component.

[0003] The administration of blood and/or blood components is common in the treatment of patients suffering from disease. Rather than infuse whole blood, it is more typical that individual components be administered to the patient(s) as their needs require. For example, administration (infusion) of platelets is often prescribed for cancer patients whose ability to make platelets has been compromised by chemotherapy. Infusion of white blood cells (i.e., mononuclear cells), after the cells have undergone some additional processing or treatment, may also be prescribed for therapeutic reasons including treatment of diseases that specifically involve the white blood cells. Thus, it is often desirable to separate and collect the desired blood component from whole blood and then treat the patient with the specific blood component. The remaining components may be returned to the donor or retained for other uses.

[0004] There are several diseases or disorders which are believed to primarily involve mononuclear cells, such as cutaneous T-cell lymphoma, organ allograft rejection after transplantation and autoimmune diseases such as rheumatoid arthritis, systemic sclerosis, among others.

[0005] Cutaneous T-cell lymphoma (CTCL) is a term that is used to describe a wide variety of disorders. Generally, CTCL is a type of cancer of the immune system where T-cells (a type of mononuclear cell) mutate or grow in an uncontrolled way, migrate to the skin and form itchy, scaly plaques or patches. More advanced stages of the disease also affect the lymph nodes. Therapeutic treatment options for CTCL have previously been limited. While chemotherapy has been utilized, this particular form of treatment also has many associated undesirable side effects, such as lowered resistance to infection, bleeding, bruising, nausea, infertility and hair loss, just to name a few.

[0006] Organ allograft rejection may be characterized as the rejection of tissues that are foreign to a host, including transplanted cardiac tissue as well as lung, liver and renal transplants. Immunosuppression drug therapy following transplantation is common. However, there are potential drawbacks including reoccurring infection due to the compromised competence of the immune system caused by this type of therapy.

[0007] Similarly, graft versus host disease (GVHD) is a complication that can occur after a stem cell or bone marrow transplant in which the newly transplanted material attacks the transplant recipient's body. The differences between the donor's cells and recipient's tissues often cause T-cells from the donor to recognize the recipient's body tissues as foreign, thereby causing the newly transplanted cells to attack the recipient. GVHD may complicate stem cell or bone marrow transplantation, thereby potentially limiting these life-saving therapies. Therefore, after a transplant, the recipient is usually administered a drug that suppresses the immune system, which helps reduce the chances or severity of GVHD. See Dugdale, David C., et al. "Graft-Versus-Host Disease," MedlinePlus A.D.A.M Medical Encyclopedia, Updated June 2, 2010.

[0008] Autoimmune diseases, including rheumatoid arthritis (RA) and progressive systemic sclerosis (PSS), can be characterized by an overactive immune system which mistakes the body's own tissues as being a foreign substance. As a result, the body makes autoantibodies that attack normal cells and tissues. At the same time, regulatory T-cells, which normally function to regulate the immune system and suppress excessive reactions or autoimmunity, fail in this capacity. This may lead to among other things, joint destruction in RA and inflammation of the connective tissue in PSS.

[0009] Where existing therapies for treating one or more diseases may result in certain unintended side effects, additional treatment may be desired or required. One known procedure which has been shown to be effective in the treatment of diseases and/or the side effects of existing therapies involving mononuclear cells is extracorporeal photopheresis or "ECP". Extracorporeal photopheresis (also sometimes referred to as extracorporeal photochemotherapy) is a process that includes: (1) collection of mononuclear cells (MNC) from a patient, (2) photoactivation treatment of the collected MNC cells; and (3) reinfusion of the treated cells (MNC) back to the patient. More specifically, ECP involves the extracorporeal exposure of peripheral blood mononuclear cells combined with a photoactive compound, such as 8-methoxypsoralen or "8-MOP" which is then photoactivated by ultraviolet light, followed by the reinfusion of the treated mononuclear cells. It is believed that the combination of 8-MOP and UV radiation causes apoptosis or programmed cell death of ECP-treated T-cells.

[0010] Although the precise mechanism of action in

ECP treatment (in the different disease states) is not fully known, according to early theories, it was believed that photoactivation causes 8-MOP to irreversibly covalently bind to the DNA strands contained in the T-cell nucleus. When the photochemically damaged T-cells are reinfused, cytotoxic effects are induced. For example, a cytotoxic T-cell or "CD8+ cell" releases cytotoxins when exposed to infected or damaged cells or otherwise attacks cells carrying certain foreign or abnormal molecules on their surfaces. The cytotoxins target the damaged cell's membrane and enter the target cell, which eventually leads to apoptosis or programmed cell death of the targeted cell. In other words, after the treated mononuclear cells are returned to the body, the immune system recognizes the dying abnormal cells and begins to produce healthy lymphocytes (T-cells) to fight against those cells.

[0011] In addition to the above, it has also been theorized that extracorporeal photopheresis also induces monocytes (a type of mononuclear cell) to differentiate into dendritic cells capable of phagocytosing and processing the apoptotic T-cell antigens. When these activated dendritic cells are re-infused into systemic circulation, they may cause a systemic cytotoxic CD8+ T-lymphocyte-mediated immune response to the processed apoptotic T-cell antigens like that described above. It will be appreciated that other possible mechanisms of action may be involved in achieving the benefits that have been observed from the ECP treatment of mononuclear cells and the subsequent benefits to patients undergoing ECP based therapies.

[0012] More recently, it has been postulated that ECP may result in an immune tolerant response in the patient. For example, in the case of graft versus-host disease, the infusion of apoptotic cells may stimulate regulatory T-cell generation, inhibit inflammatory cytokine production, cause the deletion of effective T-cells and result in other responses. See Peritt, "Potential Mechanisms of Photopheresis in Hematopoietic Stem Cell Transplantation," Biology of Blood and Marrow Transplantation 12:7-12(2006). While presently the theory of an immune tolerant response appears to be among the leading explanations, there exist other theories as to the mechanism of action of ECP relative to graft-versus-host disease, as well as other disease states.

[0013] Systems for performing ECP include, for example, the UVAR XTS Photopheresis System available from Therakos, Inc., of Exton, PA. Further details of performing ECP on the Therakos system can be found, for example, in U.S. Patent No. 5,984,887.

[0014] While the clinical benefits of ECP have been recognized, the use of ECP is not without its own drawbacks, including the systems and methods by which the ECP treatment is performed. For example, there are currently two commonly used methods for performing photopheresis - online and offline methods. In online methods, a dedicated photopheresis device, such as the Therakos device mentioned above, is used to perform the entire therapy including reinfusion of treated MNCs. Such devices are "dedicated" photopheresis devices, designed only for performing photopheresis and cannot perform other collection protocols needed in a hospital or blood processing setting including, for example, multifunctional apheresis protocols for collection of platelets, plasma, RBCs, ganulocytes and/or perform plasma/RBC exchange protocols. In offline photopheresis methods, a multifunctional apheresis device may be used to collect mononuclear cells. The collected MNCs, typically contained in one or more collection containers, are severed or otherwise separated from the tubing set used during collection, where they are later treated in a separate irradiation or UVA light device followed by manual reinfusion of the treated cells to a patient. However, during such offline methods, when the cells are transferred from the apheresis device to the irradiation device (which device may be located in another room or laboratory) communication with the donor must be severed and accordingly, the cells detached from the donor. Thus, additional traceability procedures are required to insure that the treated MNC product is ultimately reinfused into the correct donor.

[0015] Examples of systems wherein mononuclear cells are collected are known from US2010/0189597A1 and US6,027,657. An example of an irradiation device for use with a disposable fluid circuit is known from US2006/0221329A1

Therefore, it would also be desirable to develop "on line" systems and methods for providing ECP-treated mononuclear cells which avoids any additional product labeling and/or traceable handling requirements because the MNC product never leaves the disposable set which remains connected to the donor during the entire ECP treatment procedure. To this end, the systems and methods described herein include (1) a multifunctional automated apheresis device for harvesting MNCs from whole blood directly or indirectly originating from a patient and reinfusing treated MNCs directly or indirectly to a patient, (2) an irradiation device housed separately from the apheresis device which irradiates MNCs combined with 8-MOP to obtain treated MNC and (3) a disposable set which proves a sterile, closed pathway between the apheresis device and irradiation device and which remains connected to the patient during an entire photopheresis procedure. Use of a multifunctional apheresis device in accordance with the systems and methods described herein allows a hospital or medical facility to procure and maintain fewer apheresis devices, taking up less space and being more economical than having to acquire dedicated photopheresis devices used solely for performing ECP treatment, while also retaining a sterile closed pathway between two separate processing devices.

Summary

[0016] In one aspect, the present disclosure is directed to an online extracorporeal photopheresis system as

claimed in Claim 1. The system comprises a disposable fluid circuit comprising a processing chamber for separating whole blood into one or more components including mononuclear cells and at least one storage container adapted to receive mononuclear cells. At least a portion of the container is transparent to light of a selected wavelength. The system further comprises a separation device adapted to receive the processing chamber for effecting separation of mononuclear cells from whole blood and an irradiation device housed separately from the separation device adapted to receive the mononuclear cell storage container for treating the cells with a selected dose of light. The disposable fluid circuit provides a sterile closed pathway between the separation device and the irradiation device. The system further comprises a controller separate from the separation device and the irradiation device configured for communication with these devices and remote control of their operations.

[0017] In another aspect, the present disclosure is directed to control method as claimed in Claim 10 for controlling operation of the separation device and the irradiation device in the above mentioned system.

Brief Description of the Drawings

[0018]

Fig. 1 is a diagram generally showing the mechanical components of a photopheresis treatment as described herein;

Fig. 2 is a partial perspective view of a multifunctional apheresis separator useful in the methods and systems described herein;

Fig. 3 is a perspective view of a processing container (separation chamber) of the processing set used with the separator of Fig. 2;

Fig. 4 is a diagram of the fluid circuit useful in the collection, treatment and reinfusion of mononuclear cells as described herein; and

Fig. 5 is a flow chart setting forth the steps of the method of a photopheresis treatment as described herein.

Description of the Illustrated Embodiments

[0019] The subject matter of the present disclosure relates generally to systems for performing online extracorporeal photopheresis (ECP) treatment of mononuclear cells utilizing a multifunctional automated apheresis device, a disposable fluid circuit and an independent irradiation device housed separately from the apheresis device.

[0020] Fig. 1 shows, in general, the mechanical components that make up the system. In accordance with the present disclosure, the system includes a separation component 10 and a treatment (i.e., irradiation) component 20. Preferably, irradiation component 20 is independent and housed separately from separation component 10. Although separately housed and independent devices, it is preferable that separation device 10 and irradiation device 20 are located adjacent to each other. In one example, separation device 10 and irradiation 20 may be located in the same room but physically spaced several feet or yards from each other. Irradiation device 20 may be on a table top located near or adjacent to separation component 10 allowing an operator or clinician to have access to both devices during a particular treatment procedure. In accordance with the systems and described herein a patient or blood originating from a patient is connected to a blood processing set, i.e., fluid circuit 200. As generally illustrated in Figs. 1 and 4, fluid circuit 200 provides a sterile closed pathway between separation component 10 and irradiation component 20. The system described herein also optionally includes a washing component which, preferably, is housed within the separation component. Preferably, the separation component 10 and washing component are one and the same, as will be described in greater detail below.

[0021] With reference to Fig. 1, whole blood directly or indirectly withdrawn from the patient is introduced into the separation component 10 where the whole blood is separated to provide a target cell population. In a preferred embodiment in accordance with the present disclosure, the target cell population may be mononuclear cells. Other components separated from the whole blood, such as red blood cells and platelets may be returned to the patient or collected in pre-attached containers of the blood processing set.

[0022] The separated target cell population, e.g., mononuclear cells, is then treated and irradiated in treatment component 20. As discussed above, in accordance with the present disclosure, treatment of mononuclear cells involves the photoactivation of a photoactive agent that has been combined with the mononuclear cells. Once treated, the mononuclear cells may optionally be provided to a washing component, which, as shown in Fig. 1, is housed within separation component 10 and, preferably, is one and the same. The treated mononuclear cells are separated from the supernatant and the concentrated cells may be returned to the patient. The supernatant liquid will typically include excess and unbound photoactivation agent. Optionally, the concentrated cells may further be combined with a suitable wash solution within separation/washing component 10. If washing of the treated mononuclear cells is performed, the suspension of mononuclear cells in a wash solution is then subjected to a centrifugal field (or other environment which can effect separation of the fluid components), whereby the mononuclear cells are concentrated and separated from the supernatant. The supernatant liquid may include any remaining unbound photoactivation agent. Supernatant may then be diverted to an appropriate waste container, while the treated mononuclear cells are returned to the patient, as generally shown in Fig. 1.

[0023] Apparatus useful in the collection (and washing)

of mononuclear cells include the Amicus® Separator made and sold by Fenwal, Inc., of Lake Zurich, Illinois. Mononuclear cell collections using a device such as the Amicus® are described in greater detail in U.S. Patent No. 6,027,657. Preferably, the apparatus used for the harvesting, collection and reinfusion of mononuclear cells in accordance with the apparatus and methods described herein is a "multifunctional" automated apheresis device, as is the case with the Amicus® Separator. In other words, it is preferable that the separation component 10 be an multifunctional automated apparatus that can perform various collection protocols and/or serve multiple purposes, as may be needed by a particular hospital or facility, such that it can be used not only in the systems and methods for performing photopheresis treatment of MNC as described herein, but can also be used for other purposes including the collection of blood and blood components including platelets, plasma, red blood cells, granulocytes and/or perform plasma/RBC exchange, among other functions required by the hospital or medical facility. One benefit of the systems and described herein, in which a fluid processing circuit engages both a multifunctional apheresis device and an irradiation device, is that a "dedicated" photopheresis device that is designed only to perform ECP treatment, but which does not perform any other functions, is not required.

[0024] Briefly, Figs. 2-4 show a representative blood centrifuge 10 with fluid circuit 200 mounted thereon (Fig. 2), the fluid circuit (Fig. 4) having a blood processing container 14 (see Fig. 3) defining a separation chamber suitable for harvesting mononuclear cells (MNC) from whole blood. As shown in Fig. 2, a disposable processing set or fluid circuit 200 (which includes container 14) is mounted on the front panel of centrifuge 10. The processing set (fluid circuit 200) includes a plurality of processing cassettes 23L, 23M and 23R with tubing loops for association with peristaltic pumps on device 10. Fluid circuit 200 also includes a network of tubing and pre-connected containers for establishing flow communication with the patient and for processing and collecting fluids and blood and blood components, as shown in greater detail in Fig. 4. As seen in Figs. 2 and 4, disposable processing set 200 may include a container 60 for supplying anticoagulant, a waste container 62 for collecting waste from one or more steps in the process for treating and washing mononuclear cells, a container 64 for holding saline or other wash or resuspension medium, a container 66 for collecting plasma, a container 68 for collecting the mononuclear cells and, optionally, container 69 for holding the photoactivation agent.

[0025] In accordance with the systems described herein, container 68 also serves as the illumination container, and preferably, illumination container 68 is pre-attached to and integral with the disposable set 200. Alternatively, container 68 may be attached to set 200 by known sterile connection techniques, such as sterile docking or the like. In Fig. 2, container 68 is shown as suspended from device 10. However, container 68 may be housed within an adjacent separately housed irradiation device 20 (as shown by broken lines in Fig. 4), thereby eliminating the step of having the operator place container 68 into irradiation device 20. It will be appreciated that the tubing leading to and/or from container 68 in fluid circuit 200 is of a sufficient length to reach an irradiation device 20 that is adjacent to but housed separately from the separation device. In other words, regardless of whether container 68 is placed within irradiation device 20 prior to treatment or whether it is manually placed in device 20 during or after cells have been collected therein, the one or more lengths of tubing communicating with bag 68 as well as other tubing portions of fluid circuit 200 are preferably long enough to provide a sterile closed pathway between the two independent and separately housed separation device 10 and irradiation device 20 such that container 68 does not have to be separated or otherwise disconnected from the fluid circuit for cells collected therein to be treated in irradiation container 20.

[0026] With reference to Fig. 4, fluid circuit includes inlet line 72, an anticoagulant (AC) line 74 for delivering AC from container 60, an RBC line 76 for conveying red blood cells from chamber 12 of container 14 to container 67, a platelet-poor plasma (PPP) line 78 for conveying PPP to container 66 and line 80 for conveying mononuclear cells to and from separation chamber 14 and collection/illumination container 68. As will be known to those of skill in the art, the blood processing set includes one or more venipuncture needle(s) for accessing the circulatory system of the patient. As shown in Fig. 4, fluid circuit 200 includes inlet needle 70 and return needle 82. In an alternative embodiment, a single needle can serve as both the inlet and outlet needle.

[0027] Fluid flow through fluid circuit 200 is preferably driven, controlled and adjusted by a microprocessor-based controller in cooperation with the valves, pumps, weight scales and sensors of device 10 and fluid circuit 200, the details of which are described in the previously mentioned U.S. Patent No. 6,027,657.

[0028] In accordance with the present disclosure, the fluid circuit is further adapted for association with the treatment component (i.e., irradiation device) 20. Apparatus for the irradiation of the mononuclear cells are also known and are available from sources such as Cerus Corporation, of Concord, California. One example of a suitable irradiation device is described in U.S. Patent No. 7,433,030. As shown and described in U.S. Patent No. 7,433,030, irradiation device preferably includes a tray or other holder for receiving one or more containers during treatment. Other irradiation devices may also be suitable for use with the method and system described herein, including devices available from Macopharma and/or Vilber Lourmet.

[0029] As noted above, separation chamber 12 is defined by the walls of a flexible processing container 14 carried within an annular gap defined by a rotating spool element 18 and an outer bowl element (not shown). The

processing container 14 takes the form of an elongated tube which is wrapped about the spool element 18 before use. The bowl and spool element 18 are pivoted on a yoke between an upright position and a suspended position, also not shown.

[0030] When upright, the bowl and spool element 18 are presented for access by the user. A mechanism permits the spool 18 and bowl elements to be opened so that the operator can wrap the container 14 about the spool element 18, as Fig. 3 shows. Pins 150 on the spool element 18 engage cutouts on the container 14 to secure the container 14 on the spool element 18. In operation, the centrifuge 10 rotates the suspended bowl and spool element 18 about an axis 28, creating a centrifugal field within the processing chamber of container 14.

[0031] The radial boundaries of the centrifugal field are formed by the interior wall of the bowl element and the exterior wall 26 of the spool element 20. The interior bowl wall defines the high-G wall. The exterior spool wall 26 defines the low-G wall. Further details of the mechanism for causing relative movement of the spool 18 and bowl elements as just described are disclosed in U.S. Patent No. 5,360,542 entitled "Centrifuge With Separable Bowl and Spool Elements Providing Access to the Separation Chamber,".

[0032] Turning now to the method of treating mononuclear cells, as shown in Fig. 5, whole blood directly or indirectly withdrawn from a patient (step 30) through inlet needle 70 is introduced into the separation chamber 12 of container 14 of processing set 200, where the whole blood is subjected to a centrifugal field. The centrifugal field will separate the target cell population, i.e., mononuclear cells, from red blood cells, platelets and plasma (step 32). As discussed above, the components such as red blood cells and platelets may be returned to the patient or may be diverted to a container (e.g., container 67) for further processing.

[0033] Collection of the mononuclear cells may proceed in one or more cycles. The number of processing cycles conducted in a given therapeutic procedure will depend upon the total volume of MNC to be collected. For example, in a representative procedure, five collection cycles may be performed sequentially. During each cycle about 1500-3000 ml of whole blood can be processed to obtain a MNC volume of about 3 ml per cycle and a total volume of 15 ml of MNC. As shown in step 32 of Fig. 5, the final volume of mononuclear cells is then provided for further treatment in accordance with the present disclosure. Of course, the collection of MNC is not limited to the method described above. MNCs may be collected in any manner known to those of skill in the art, but preferably using a multifunctional apheresis device.

[0034] Effective treatment of the mononuclear cells with light may require that the amount of collected mononuclear cells have a suitable hematocrit. Thus, it may be desired or even necessary to dilute the mononuclear cells with a diluting solution such as plasma or saline, as shown in step 33. In the example described above, approximately 15 ml of MNC may be diluted in about 200 ml of plasma.

[0035] The diluted mononuclear cells (in container 68) are then combined with the suitable photoactivation agent in step 34. Alternatively, the desired volume of the agent may be pre-added to the container. As discussed above, for ECP treatment, the compound 8-methoxypsoralen (8-MOP) has been shown to be an effective photoactivation agent. However, other suitable photoactivation agents may be used, including, for example, a psoralen compound. In one example, the system, under the direction of the microprocessor-based controller, may be programmed to automatically deliver the desired amount of photoactive agent from, for example, container 69 before or after the MNC collection, based on the volume of MNC collected or to be collected. For example, 8-MOP may be pre-added to container 68 at the beginning of a particular procedure or alternatively, added to the MNCs collected in the container just prior to irradiation. The 8-MOP is combined with the collected and diluted mononuclear cells to arrive at a mixture having a final 8-MOP concentration of 200 nanograms/mL and/or any effective amount. Typically, the mononuclear cells may be combined with the photoactivation agent to arrive at a final 8-MOP concentration in a range of about 100 to 300 nanograms/mL. The 8-MOP or other photoactivation agent may be added directly to container 68 by a syringe through a port in the container, or added elsewhere in fluid circuit 200 also by a syringe.

[0036] As noted above, the mononuclear cells collected in accordance with the mononuclear cell collection process described above may be collected in container 68 that is suitable for irradiation by light of a selected wavelength. By "suitable" it is meant that the walls of the container are sufficiently transparent to light of the selected wavelength to activate the photoactive agent. In treatments using UVA light, for example, container walls made of ethylene vinyl acetate (EVA) are suitable. Accordingly, container 68 in which the mononuclear cells are collected may serve both as the collection container and the irradiation container. Container 68 may placed inside irradiation device 20 by the operator or more preferably, may be placed inside the irradiation chamber of irradiation device 20 at the beginning of the ECP procedure and prior to whole blood withdrawal (as shown by the broken lines representing device 20 in Fig. 4). In any event, container 68 preferably remains integrally connected to the remainder of fluid circuit 200 during the entire procedure, thereby maintaining the closed or functionally closed condition of fluid circuit 200.

[0037] As noted above, the fluid circuit 200 is adapted for association with the separation device 10 and with the treatment component (i.e., irradiation device) 20. It will be appreciated that the irradiation device does not have to be integral or even associated with the separation device 10. In fact, the irradiation device 20 is preferably an "adjunct" or independently housed irradiation device

20 used to perform the photopheresis therapy and located adjacent to or in a spaced-apart location from device 10. However, the disposable set 200 (including irradiation container 68) remains connected to the patient during the entire ECP treatment procedure and provides a sterile closed pathway between separation device 10 and the irradiation device 20.

[0038] Operation of both separation device 10 and irradiation device 20 and the process steps carried out by each is remotely controlled by a separate controller (e.g., a computer) that communicates with both.

[0039] The mononuclear cells with photoactivation agent (8-MOP) are then irradiated for a selected period of time (step 36). In one non-limiting example, during treatment, the mononuclear cell product may be exposed to UV bulbs having a wavelength in the UVA range of about 320 nm to 400 nm for a selected period of time, such as approximately 10-60 minutes, resulting in an average UVA exposure of approximately 0.5-5.0 J/cm^2 and use preferably approximately 1-2 J/cm^2 or even more preferably approximately 1.5 J/cm^2 per lymphocyte.

[0040] Once treatment is complete, the treated mononuclear cells may be returned to separator 10 (and more specifically, the separation chamber 12 of container 14) as shown in step 38 of Fig. 5. For example, one of the pumps associated with cassette 23R may be actuated (automatically by the controller or under the manual control of the operator) to withdraw the treated MNC from container 68 and introduce the MNC into chamber 12 of container 14. Once inside chamber 12, the MNC may be concentrated (step 40). Supernatant, which will include unbound photoactivation agent is separated from the concentrated and treated cells and diverted to a waste container.

[0041] Concentrating treated MNCs prior to reinfusion allows for the concentrated cells to have a smaller total volume as compared to un-concentrated cells, and as a result, a smaller volume of concentrated MNCs may be reinfused to a patient faster. The concentrated cells may be resuspended in a suitable resuspension medium (e.g., plasma, saline) as shown in step 43 and directly or indirectly returned to the patient. Optionally, prior to direct or indirect return to the patient, the concentrated and treated cells may be combined with a suitable wash solution (step 42), supplied (by the pumping action of pumps associated with cassette 23R) from containers 66 and/or 64 (see Fig. 4) is added to the concentrated cells.

[0042] Where the concentrated cells are optionally combined with wash solution (as per step 42), the mononuclear cells with wash solution within the chamber 12 (of container 14 of the disposable processing set 200) are subjected to a centrifugal field. The MNC are separated from remaining supernatant (step 44) under the field of centrifugal force. Any remaining unbound and excess photoactive agent will be separated from the concentrated mononuclear cells and suspended in the supernatant. The supernatant may then be withdrawn to a waste container 62 (Fig. 4) while the concentrated and washed mononuclear cells may be resuspended with a resuspension solution (such as, but not limited to, plasma or saline) as shown in step 45, and returned back to the patient, as shown in step 46 of Fig. 5. It will be appreciated that the step of washing the mononuclear cells may be repeated, as necessary. Solutions suitable for washing mononuclear cells include saline, plasma, or any other solution that is compatible with the mononuclear cell apheresis.

[0043] It will also be appreciated that the steps described above are preferably performed with the patient or a source of biological fluid, such as blood, continuously connected to the system. In that regard, the entire treatment, including the washing of the MNC, is deemed to be an "on-line" procedure. Thus, in accordance with the systems and methods described herein, a multifunctional apheresis device 10, a disposable set 200 and an independent irradiation device 20 may be used to perform an online ECP treatment procedure. More specifically, a multifunctional apheresis device 10 is preferably used to collect MNCs from a patient and transfer the MNCs to an irradiation container 68 which is pre-attached or sterile connected to disposable set 200. MNCs combined with 8-MOP in container 68 are irradiated in device 20 resulting in treated MNCs. The treated MNC are conveyed through the disposable set 200 back into device 10 for reinfusion to the patient, all while at least a portion of the disposable set 200 remains connected to the donor, thus maintaining a closed "online" ECP treatment.

[0044] As previously mentioned, the online nature of the systems and methods described herein avoid the necessity for additional MNC product labeling or handling, as the mononuclear cells never leave the disposable set (and irradiation container 68 is never disconnected from the set) during the entire ECP treatment procedure. In other words, the disposable set 200 provides a sterile, closed pathway between the multifunctional apheresis device 10 and the irradiation device 20 such that from the time MNCs are harvested from the patient, to the time that the ECP treated MNCs are reinfused to the patient, an online closed system is maintained and reinfusion to the correct patient is ensured.

[0045] In a further embodiment, it may be desirable to cryopreserve at least a portion of fresh ECP treated and washed cells that remain after a selected volume (i.e., a single therapeutic dose) of treated cells are administered to a patient.

Claims

1. An online extracorporeal photopheresis system comprising:

   (a) a disposable fluid circuit (200) comprising:

      i. a processing chamber (12) for separating whole blood into one or more components

including mononuclear cells,
ii. at least one storage container (68) adapted to receive mononuclear cells wherein at least a portion of said container (68) is transparent to light of a selected wavelength,

(b) a separation device (10) adapted to receive said processing chamber (12) for effecting separation of said mononuclear cells from whole blood, the processing chamber (12) being mounted thereon,
(c) an irradiation device (20) housed separately from said separation device (10), and adapted to receive said mononuclear cell storage container for treating said mononuclear cells with a selected dose of light, the storage container (68) being mounted thereon;
(d) a controller separate from the separation device (10) and the irradiation device (20) and configured for communication therewith, so that operation of both the separation device (10) and the irradiation device (20) can be remotely controlled by the controller;

wherein said disposable fluid circuit (200) provides a sterile closed pathway between the separation chamber (12) mounted in said separation device (10) and said storage container (68) mounted in irradiation device (20).

2. The system of Claim 1, wherein the system is configured for returning treated mononuclear cells from the storage container (68) to said separation chamber (12) for concentration into a concentrate of said treated cells, wherein supernatant is separated from the concentrated and treated cells to a waste container.

3. The system of Claim 2 wherein said separation device comprises a centrifugation device.

4. The system of Claim 3, wherein the system is configured for combining the concentrated and treated cells with a wash solution in the centrifugation device.

5. The system of Claim 4, wherein the disposable circuit is further provided with at least one container (64, 66) adapted to contain a wash solution, and with a plurality of processing cassettes (23L, 23M, 23R) with tubing loops for association with peristaltic pumps, and wherein at least one peristaltic pump is present that is associated with a processing cassette (23R), wherein the system is configured for supplying the wash solution by pumping action of the peristaltic pump from the container (64, 66) adapted to contain wash solution.

6. The system of Claim 5, wherein the said peristaltic pump is actuated by the controller.

7. The system as claimed in any of the preceding claims, wherein the system is programmed, under the direction of the controller, to automatically deliver a desired amount of photoactive agent from a container (69) before or after collection of mononuclear cells into the storage container (68).

8. The system as claimed in any of the preceding claims, wherein the irradiation treatment is carried out with UVA light, and the storage container (68) has container walls made of ethylene vinyl acetate (EVA).

9. The system as claimed in any of the preceding claims, wherein the system is configured for dilution of collected mononuclear cells with a diluting solution, so that the amount of collected mononuclear cells in the storage container have a suitable hematocrit for the treatment with light to be effective.

10. A control method for controlling operation of a separation device (10) and a irradiation device (20) that are housed separately and are part of an online extracorporeal photopheresis system provided with a disposable fluid circuit (200) comprising a processing chamber (12) and at least one storage container (68), wherein at least a portion of said container (68) is transparent to light of a selected wavelength, wherein said processing chamber (12) is mounted on the separation device (10) for effecting separation of said mononuclear cells from whole blood, and wherein said storage container (68) is mounted on the irradiation device (20) for treating said mononuclear cells with a selected dose of light, wherein said disposable fluid circuit (200) provides a sterile closed pathway between the separation chamber (12) mounted in said separation device (10) and said storage container (68) mounted in irradiation device (20), and wherein a separate controller is present,
wherein said control method comprises remotely controlling operation of both the separation device (10) and the irradiation device (20) by the controller that communicates with both.

11. The control method of Claim 10, wherein said control method further comprising controlling automatic delivery a desired amount of photoactive agent from a container (69) thereof, to the storage container (68) before or after collection of mononuclear cells in the storage container (68).

12. The control method as claimed in Claim 11, wherein the desired amount is determined based on the volume of mononuclear cells collected or to be collected.

13. The control method as claimed in any of the Claims 10-12, wherein said control method further comprises control of actuation of a peristaltic pump associated with a processing cassette (23R) of the disposable fluid circuit to withdraw treated mononuclear cells from the storage container (68) and to introduce these mononuclear cells into the processing chamber (12) of a processing container (14).

Patentansprüche

1. System für gekoppelte extrakorporale Photopherese, das aufweist:

(a) einen Wegwerffluidkreislauf (200), der aufweist:

i. eine Verarbeitungskammer (12) zum Abscheiden von Vollblut in eine oder mehrere Komponenten einschließlich mononuklearer Zellen,
ii. wenigstens einen Lagerbehälter (68), der geeignet ist, mononukleare Zellen aufzunehmen, wobei wenigstens ein Abschnitt des Behälters (68) für Licht einer ausgewählten Wellenlänge transparent ist,

(b) eine Abscheidungsvorrichtung (10), die geeignet ist, die Verarbeitungskammer (12) aufzunehmen, um die Abscheidung der mononuklearen Zellen aus dem Vollblut herbeizuführen, wobei die Verarbeitungskammer (12) darauf montiert ist,
(c) eine Bestrahlungsvorrichtung (20), die getrennt von der Abscheidungsvorrichtung (10) untergebracht ist und geeignet ist, den Lagerbehälter für mononukleare Zellen aufzunehmen, um die mononuklearen Zellen mit einer ausgewählten Lichtdosis zu behandeln, wobei der Lagerbehälter (68) darauf montiert ist;
(d) eine Steuerung getrennt von der Abscheidungsvorrichtung (10) und der Bestrahlungsvorrichtung (20), die für die Kommunikation mit diesen konfiguriert ist, so dass der Betrieb sowohl der Abscheidungsvorrichtung (10) als auch der Bestrahlungsvorrichtung (20) durch die Steuerung ferngesteuert werden können;

wobei der Wegwerffluidkreislauf (200) eine sterile geschlossene Leitung zwischen der in der Abscheidungsvorrichtung (10) montierten Abscheidungskammer (12 und dem in der Strahlungsvorrichtung (20) montierten Lagerbehälter (68) bereitstellt.

2. System nach Anspruch 1, wobei das System konfiguriert ist, um behandelte mononukleare Zellen von dem Lagerbehälter (68) für eine Konzentration in ein Konzentrat der behandelten Zellen an die Abscheidungskammer (12) zurückzuführen, wobei Überstand von den konzentrierten und behandelten Zellen in einen Abfallbehälter abgeschieden wird.

3. System nach Anspruch 2, wobei die Abscheidungsvorrichtung eine Zentrifugiervorrichtung aufweist.

4. System nach Anspruch 3, wobei das System konfiguriert ist, um die konzentrierten und behandelten Zellen in der Zentrifugiervorrichtung mit einer Spüllösung zu kombinieren.

5. System nach Anspruch 4, wobei der Wegwerfkreislauf ferner mit wenigstens einem Behälter (64, 66), der geeignet ist, eine Spüllösung zu enthalten, und mit mehreren Verarbeitungskassetten (23L, 23M, 23R) mit Schlauchschleifen für die Verbindung mit peristaltischen Pumpen versehen ist, wobei wenigstens eine peristaltische Pumpe vorhanden ist, die mit einer Verarbeitungskassette (23R) verbunden ist, wobei das System konfiguriert ist, um die Spüllösung durch die Pumpwirkung der peristaltischen Pumpe von dem Behälter (64, 66), der geeignet ist, um Spüllösung zu enthalten, zuzuführen.

6. System nach Anspruch 5, wobei die peristaltische Pumpe durch die Steuerung betätigt wird.

7. System nach einem der vorhergehenden Ansprüche, wobei das System unter der Leitung der Steuerung programmiert ist, um vor oder nach dem Sammeln der mononuklearen Zellen in den Lagerbehälter (68) automatisch eine gewünschte Menge eines fotoaktiven Mittels aus einem Behälter (69) zu liefern.

8. System nach einem der vorhergehenden Ansprüche, wobei die Bestrahlungsbehandlung mit UVA-Licht ausgeführt wird und der Lagerbehälter (68) aus Ethylenvinylacetat (EVA) hergestellte Behälterwände hat.

9. System nach einem der vorhergehenden Ansprüche, wobei das System für die Verdünnung mononuklearer Zellen mit einer Verdünnungslösung konfiguriert ist, so dass die Menge gesammelter mononuklearer Zellen in dem Lagerbehälter einen geeigneten Hämatokriten hat, so dass die Behandlung mit Licht wirksam ist.

10. Steuerverfahren zur Steuerung des Betriebs einer Abscheidungsvorrichtung (10) und einer Bestrahlungsvorrichtung (20), die getrennt untergebracht sind und Teil eines Systems für gekoppelte extrakorporale Photopherese sind, das mit einem Wegwerffluidkreislauf (200) versehen ist, der eine Verarbeitungskammer (12) und wenigstens einen Lager-

behälter (68) aufweist, wobei wenigstens ein Abschnitt des Behälters (68) für Licht einer ausgewählten Wellenlänge transparent ist, wobei die Verarbeitungskammer (12) auf die Abscheidungsvorrichtung (10) montiert ist, um die Abscheidung mononuklearer Zellen aus Vollblut herbeizuführen, und wobei der Lagerbehälter (68) auf der Bestrahlungsvorrichtung (20) zum Behandeln der mononuklearen Zellen mit einer ausgewählten Lichtdosis montiert ist, wobei der Wegwerffluidkreislauf (200) eine sterile geschlossene Leitung zwischen der in der Abscheidungsvorrichtung (10) montierten Abscheidungskammer (12) und dem in der Strahlungsvorrichtung (20) montierten Lagerbehälter (68) bereitstellt, und wobei eine getrennte Steuerung vorhanden ist,
wobei das Steuerverfahren den Fernsteuerungsbetrieb sowohl der Abscheidungsvorrichtung (10) als auch der Bestrahlungsvorrichtung (20) durch die Steuerung, die mit beiden kommuniziert, aufweist.

11. Steuerverfahren nach Anspruch 10, wobei das Steuerverfahren ferner das Steuern der automatischen Lieferung einer gewünschten Menge eines fotoaktiven Mittels aus einem Behälter (69) damit an den Lagerbehälter (68) vor oder nach dem Sammeln mononuklearer Zellen in dem Lagerbehälter (68) aufweist.

12. Steuerverfahren nach Anspruch 11, wobei die gewünschte Menge basierend auf dem Volumen mononuklearer Zellen, das gesammelt wird oder gesammelt werden soll, bestimmt wird.

13. Steuerverfahren nach einem der Ansprüche 10 - 12, wobei das Steuerverfahren ferner die Steuerung der Betätigung der peristaltischen Pumpe, die mit einer Verarbeitungskassette (23R) des Wegwerffluidkreislaufs verbunden ist, aufweist, um behandelte mononukleare Zellen aus dem Lagerbehälter (68) zu entnehmen und diese mononuklearen Zellen in die Verarbeitungskammer (12) eines Verarbeitungsbehälters (14) einzuleiten.

Revendications

1. Système de photophérèse extracorporelle en ligne comprenant :

(a) un circuit de fluide jetable (200) comprenant :

i. une chambre de travail (12) permettant de séparer du sang total en un ou plusieurs constituants incluant des cellules mononucléées,
ii. au moins un contenant de stockage (68) adapté pour recevoir des cellules mononucléées dans lequel au moins une portion dudit contenant (68) est transparente à un rayonnement d'une longueur d'onde sélectionnée,

(b) un dispositif de séparation (10) adapté pour recevoir ladite chambre de travail (12) permettant d'effectuer une séparation desdites cellules mononuclées à partir de sang total, la chambre de travail (12) étant montée sur celui-ci,
(c) un dispositif d'irradiation (20) abrité séparément dudit dispositif de séparation (10), et adapté pour recevoir ledit contenant de stockage de cellules mononuclées permettant de traiter lesdites cellules mononuclées avec une dose sélectionnée de rayonnement, le contenant de stockage (68) étant monté sur celui-ci ;
(d) un dispositif de commande séparé du dispositif de séparation (10) et du dispositif d'irradiation (20) et configuré pour une communication avec ceux-ci, de sorte qu'un fonctionnement à la fois du dispositif de séparation (10) et du dispositif d'irradiation (20) puisse être commandé à distance par le dispositif de commande ;

dans lequel ledit circuit de fluide jetable (200) fournit une voie fermée stérile entre la chambre de séparation (12) montée dans ledit dispositif de séparation (10) et ledit contenant de stockage (68) monté dans le dispositif d'irradiation (20).

2. Système selon la revendication 1, dans lequel le système est configuré pour renvoyer des cellules mononuclées traitées depuis le contenant de stockage (68) jusqu'à ladite chambre de séparation (12) pour une concentration en un concentré desdites cellules traitées, dans lequel un surnageant est séparé des cellules concentrées et traitées jusqu'à un contenant à déchets.

3. Système selon la revendication 2 dans lequel ledit dispositif de séparation comprend un dispositif de centrifugation.

4. Système selon la revendication 3, dans lequel le système est configuré pour combiner les cellules concentrées et traitées avec une solution de lavage dans le dispositif de centrifugation.

5. Système selon la revendication 4, dans lequel le circuit jetable est en outre pourvu d'au moins un contenant (64, 66) adapté pour contenir une solution de lavage, et d'une pluralité de cassettes de travail (23L, 23M, 23R) avec des boucles de tubulure pour une association avec des pompes péristaltiques, et dans lequel au moins une pompe péristaltique est présente qui est associée à une cassette de travail (23R), dans lequel le système est configuré pour fournir la solution de lavage par une action de pompage de la

pompe péristaltique à partir du contenant (64, 66) adapté pour contenir une solution de lavage.

6. Système selon la revendication 5, dans lequel ladite pompe péristaltique est actionnée par le dispositif de commande.

7. Système selon l'une quelconque des revendications précédentes, dans lequel le système est programmé, sous la direction du dispositif de commande, pour délivrer automatiquement une quantité désirée d'agent photoactif à partir d'un contenant (69) avant ou après une collecte de cellules mononuclées dans le contenant de stockage (68).

8. Système selon l'une quelconque des revendications précédentes, dans lequel le traitement d'irradiation est réalisé avec un rayonnement UVA, et le contenant de stockage (68) a des parois de contenant fabriquées en éthylène-acétate de vinyle (EVA).

9. Système selon l'une quelconque des revendications précédentes, dans lequel le système est configuré pour une dilution de cellules mononuclées collectées avec une solution de dilution, de sorte que la quantité de cellules mononuclées collectées dans le contenant de stockage ait un hématocrite adéquat pour que le traitement avec un rayonnement soit efficace.

10. Procédé de commande permettant de commander un fonctionnement d'un dispositif de séparation (10) et d'un dispositif d'irradiation (20) qui sont abrités séparément et font partie d'un système de photophérèse extracorporelle en ligne pourvu d'un circuit de fluide jetable (200) comprenant une chambre de travail (12) et au moins un contenant de stockage (68), dans lequel au moins une portion dudit contenant (68) est transparente à un rayonnement d'une longueur d'onde sélectionnée, dans lequel ladite chambre de travail (12) est montée sur le dispositif de séparation (10) permettant d'effectuer une séparation desdites cellules mononuclées à partir de sang total, et dans lequel ledit contenant de stockage (68) est monté sur le dispositif d'irradiation (20) permettant de traiter lesdites cellules mononuclées avec une dose sélectionnée de rayonnement, dans lequel ledit circuit de fluide jetable (200) fournit une voie fermée stérile entre la chambre de séparation (12) montée dans ledit dispositif de séparation (10) et ledit contenant de stockage (68) monté dans le dispositif d'irradiation (20), et dans lequel un dispositif de commande séparé est présent,
dans lequel ledit procédé de commande comprend une commande à distance d'un fonctionnement à la fois du dispositif de séparation (10) et du dispositif d'irradiation (20) par le dispositif de commande qui communique avec les deux.

11. Procédé de commande selon la revendication 10, dans lequel ledit procédé de commande comprend en outre la commande d'une délivrance automatique d'une quantité désirée d'agent photoactif à partir d'un contenant (69) de celui-ci, au contenant de stockage (68) avant ou après une collecte de cellules mononuclées dans le contenant de stockage (68).

12. Procédé de commande selon la revendication 11, dans lequel la quantité désirée est déterminée sur la base du volume de cellules mononuclées collectées ou devant être collectées.

13. Procédé de commande selon l'une quelconque des revendications 10 à 12, dans lequel ledit procédé de commande comprend en outre la commande d'un actionnement d'une pompe péristaltique associée à une cassette de travail (23R) du circuit de fluide jetable pour retirer des cellules mononuclées traitées du contenant de stockage (68) et pour introduire ces cellules mononuclées dans la chambre de travail (12) d'un contenant de travail (14).

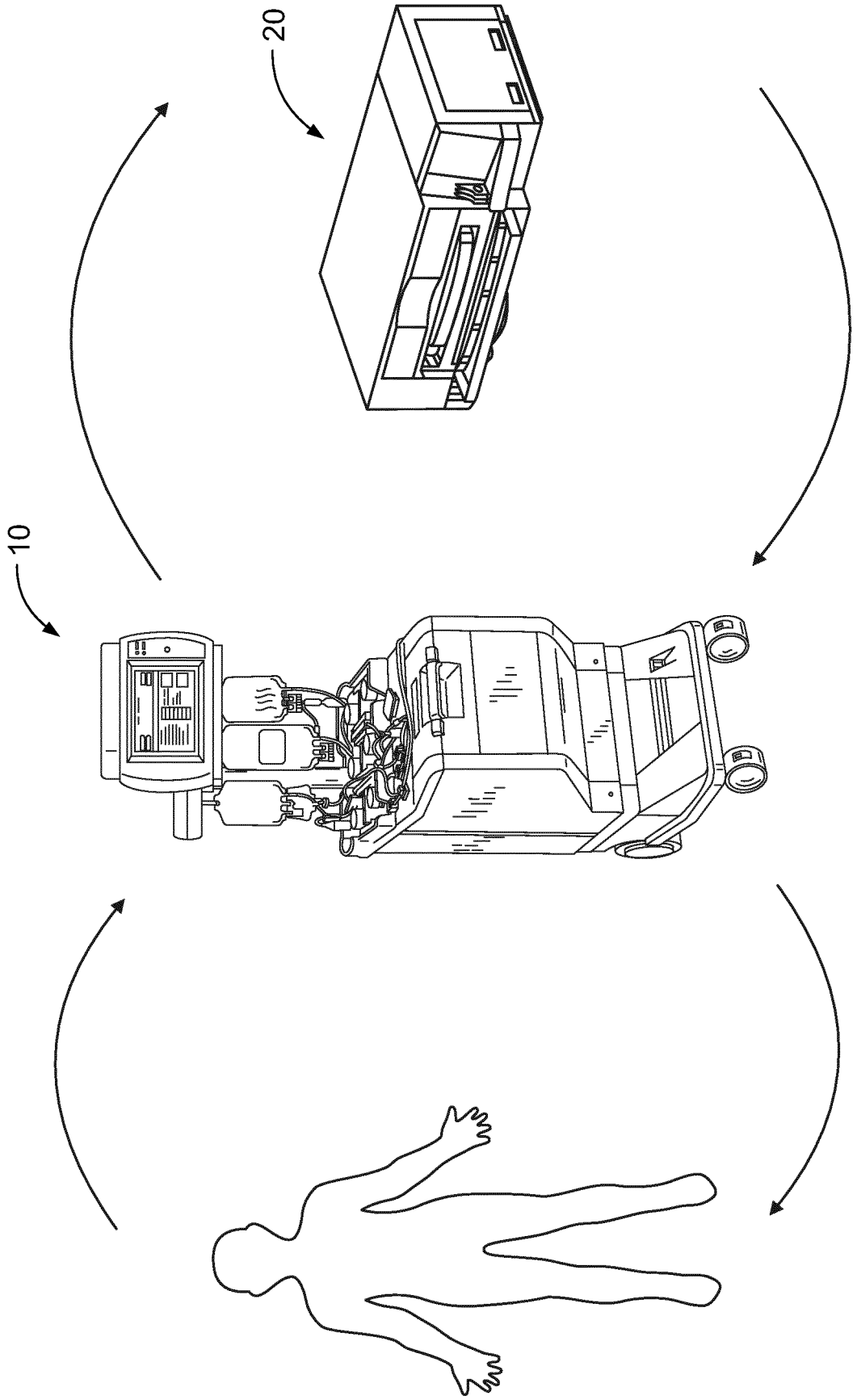

FIG. 1

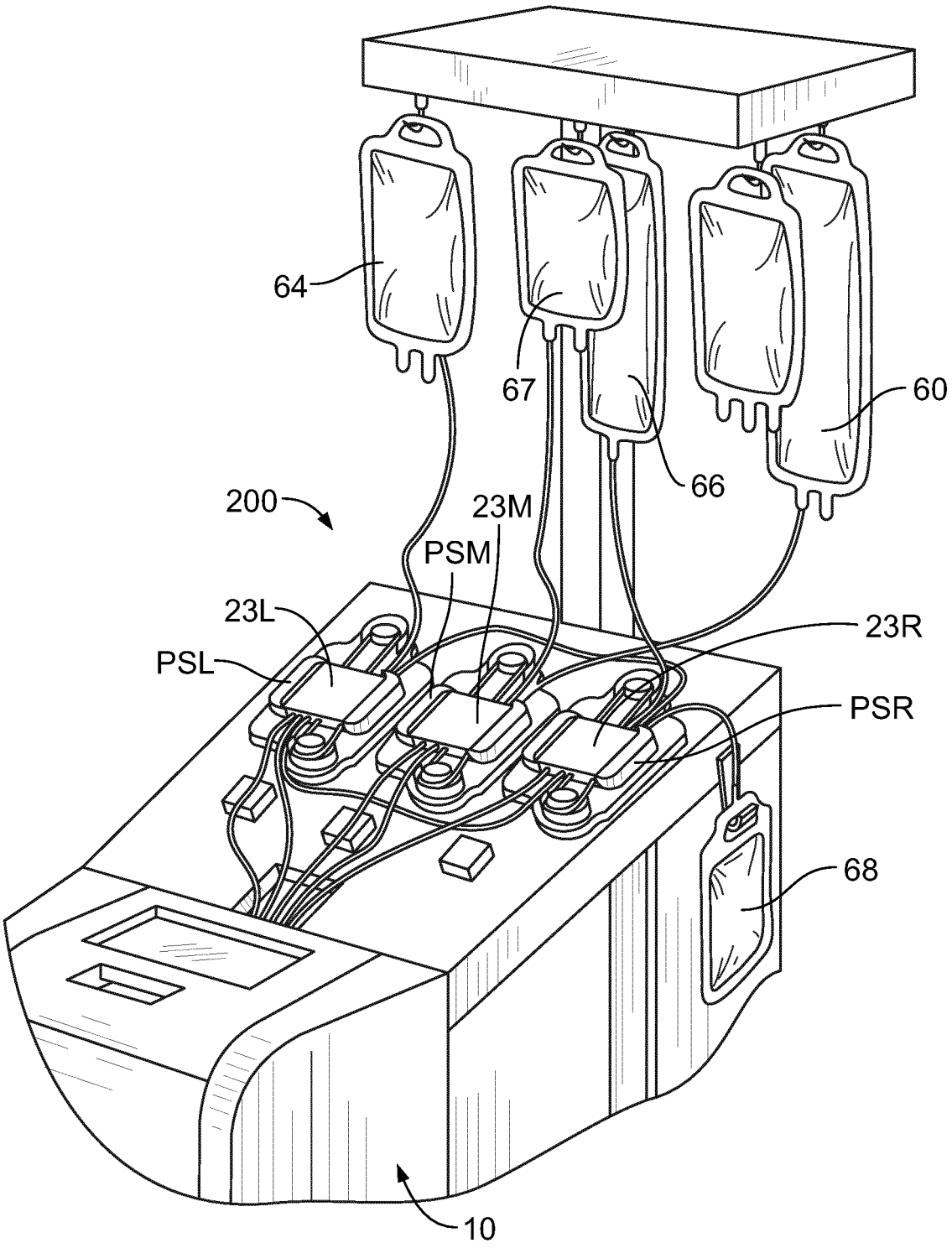

FIG. 2

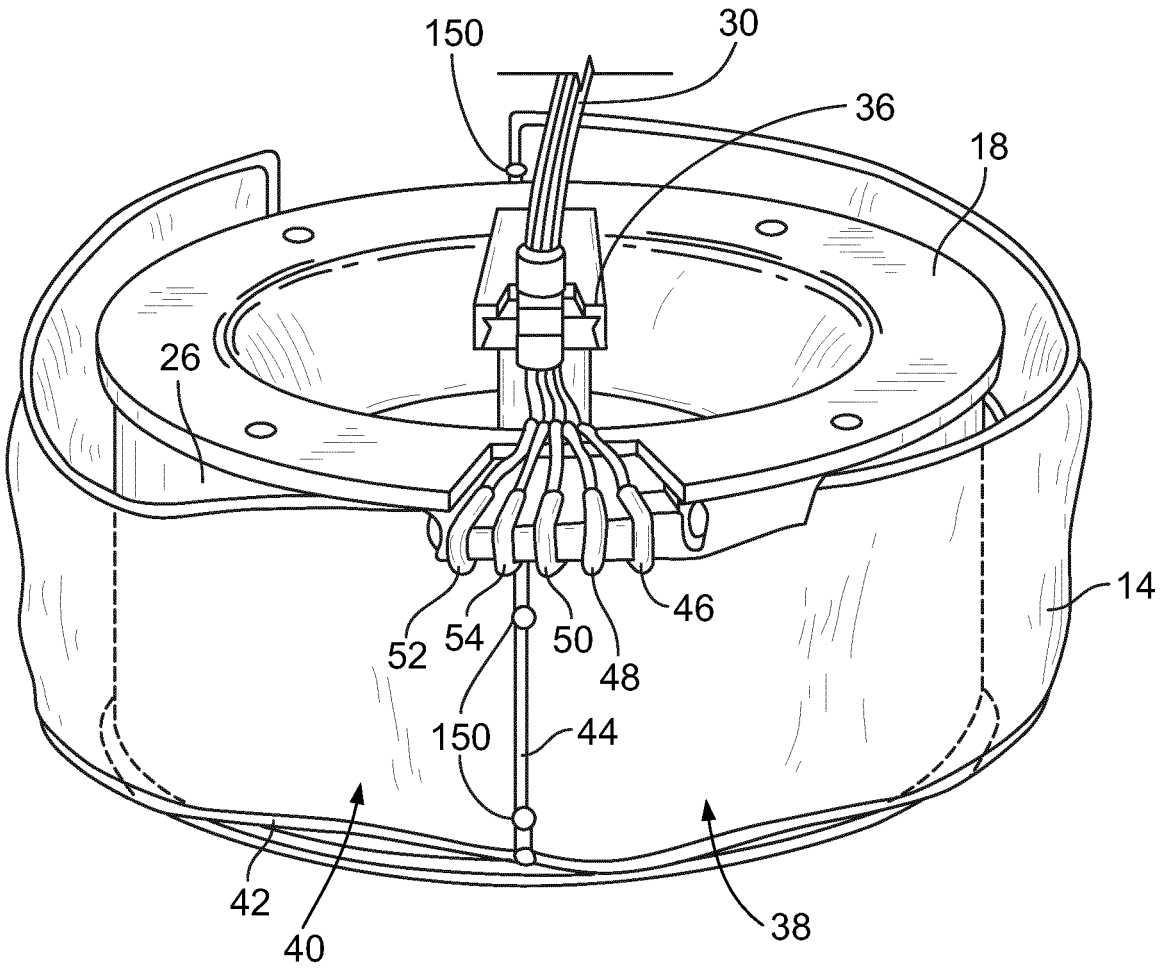

FIG. 3

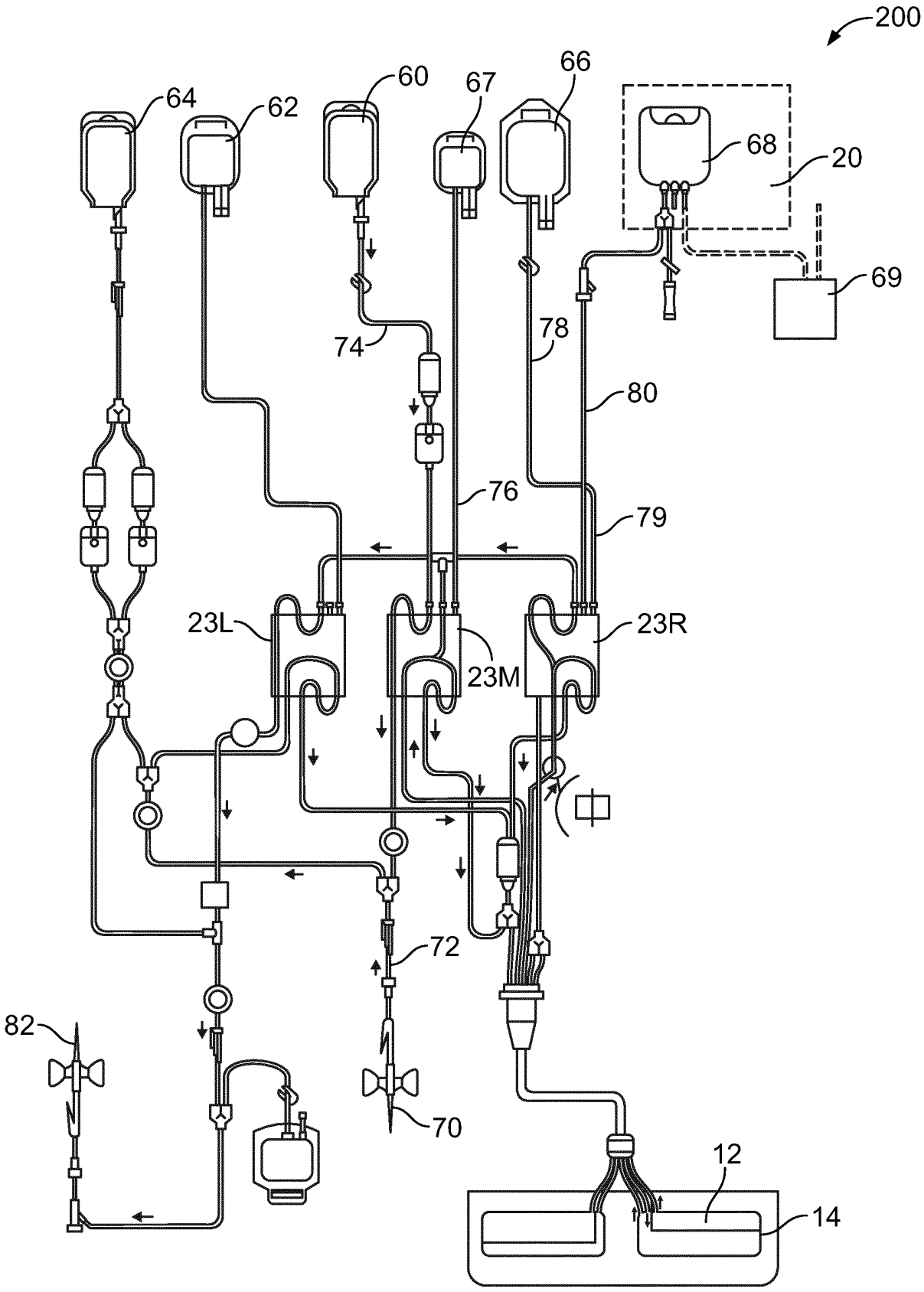

FIG. 4

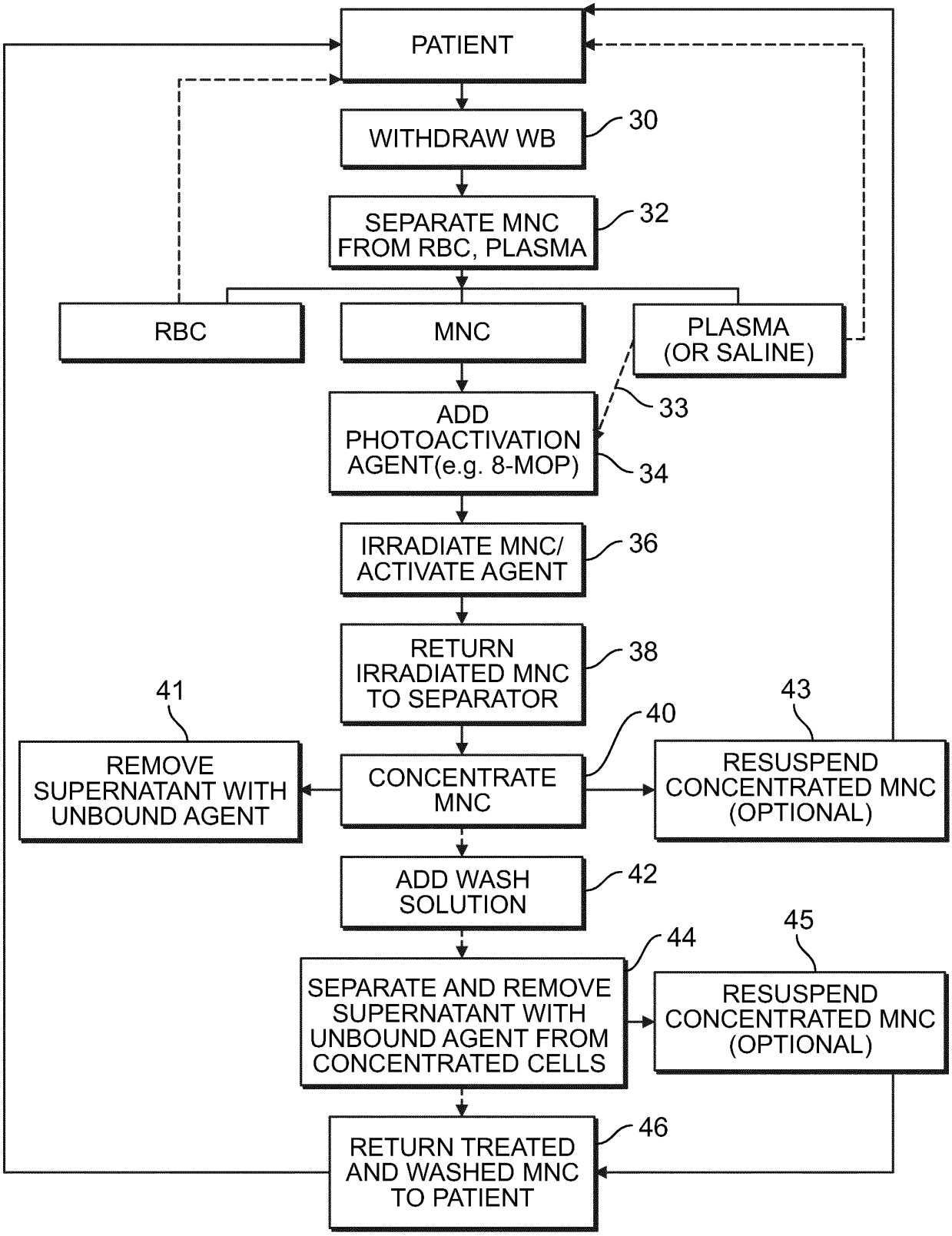
PATIENT
WITHDRAW WB
30
SEPARATE MNC FROM RBC, PLASMA
32
RBC
MNC
PLASMA (OR SALINE)
33
ADD PHOTOACTIVATION AGENT(e.g. 8-MOP)
34
IRRADIATE MNC/ ACTIVATE AGENT
36
RETURN IRRADIATED MNC TO SEPARATOR
38
41
43
40
REMOVE SUPERNATANT WITH UNBOUND AGENT
CONCENTRATE MNC
RESUSPEND CONCENTRATED MNC (OPTIONAL)
ADD WASH SOLUTION
42
45
44
SEPARATE AND REMOVE SUPERNATANT WITH UNBOUND AGENT FROM CONCENTRATED CELLS
RESUSPEND CONCENTRATED MNC (OPTIONAL)
RETURN TREATED AND WASHED MNC TO PATIENT
46

FIG. 5

REFERENCES CITED IN THE DESCRIPTION

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